Development of Toxicity Values for GenX and PFBS

Briefing #1 to Stakeholders

US EPA

March 9, 2018

Purpose of the Briefing:

- Provide stakeholders (including States and other federal agencies) periodic updates on the status of EPA's development of toxicity values for two PFAS chemicals
  - GenX – assessment led by EPA Office of Water and Office of Pollution Prevention and Toxics
  - PFBS – assessment led by EPA Office of Research and Development

Overall Scientific Objectives

- Provide the health effects information for the development of standard toxicity values (oral reference dose, cancer slope factor where possible) including the science-based decisions providing the basis for estimating the point of departure (POD)

Plan for Stakeholder Engagement:

- Stakeholder Update # 1 – problem formulation and review of available information
- Stakeholder Update #2 – overview of analysis, including effects characterization and derivation of draft toxicity values
- External peer review
- Stakeholder Update #3 – Summary of external peer review comments, Agency response, and determination of final toxicity values
- Public meeting to present the final values and discuss risk communication

Proposed Document Structure

- Background
  - Nature of the stressor including occurrence, chemical and physical properties and toxicokinetics
- Problem Formulation
  - Conceptual model
  - Overall Scientific Objectives
  - Methods including the literature search strategy and study evaluation processes
  - Approach for Derivation of Reference Values (e.g., effect level identification; Benchmark Dose modeling)
- Study Synthesis and Health Effects Characterization
- Derivation of Reference Value(s)

GenX

Nature of the Stressor

Timeline

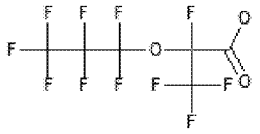
- 2006: EPA initiated the PFOA Stewardship Program to eliminate chemical emissions of PFOA and related chemicals by 2015.
- 2006: DuPont/Chemours committed to this stewardship.
- 2008: DuPont submitted two premanufacture notices for GenX chemicals.
- 2008: EPA conducted initial risk assessment on these chemicals.
- 2009: EPA issues Consent Order DuPont/Chemours, to conduct additional health effects studies, among other things.
- Chemours conducts additional studies.
- 2015: New PFAS identified in Cape Fear River, NC
- 2016: GenX chemicals were measured in drinking water in North Carolina.
- 2017: North Carolina DEQ orders Chemours to stop discharging GenX chemicals.
- 2018: EPA is deriving an RfD for GenX chemicals.

Nature of the Stressor

What is GenX?

- GenX is a trade name for a processing aid technology developed by DuPont/Chemours
  - Enables the manufacture of fluoropolymers without the use of PFOA
- HFPO dimer acid and its ammonium salt are the two major chemicals associated with the GenX processing aid technology:

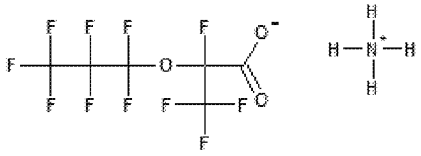
CAS# 13252-13-6



Propanoic acid, 2,3,3,3-tetrafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)-

HFPO dimer acid

CAS# 62037-80-3



Propanoic acid, 2,3,3,3-tetrafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)-, ammonium salt (1:1)

HFPO dimer acid ammonium salt

Nature of the Stressor

Occurrence

North Carolina

- Chemours had National Pollutant Discharge Elimination System (NPDES) permit to discharge HFPO dimer in wastewater
  - Most recent NPDES permit: July 1, 2015 - October 31, 2016
- Surface Water
  - Strynar et al., 2015
  - Sun et al., 2016
- Ground Water
  - NC DEQ had Chemours test private wells
- Drinking Water
  - Sun et al., 2016

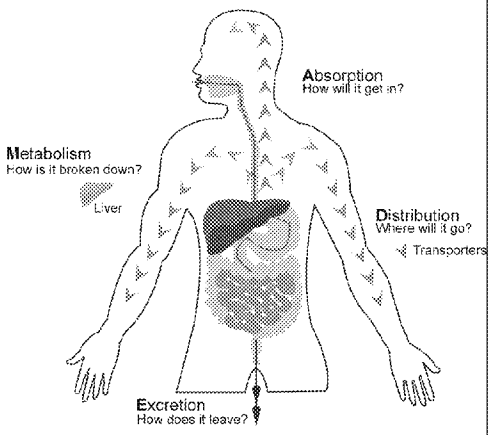
West Virginia

- Chemours has had a NPDES permit to discharge HFPO dimer through at least 2011
  - Current status of NPDES permit unknown
- EPA requested Chemours to test for HFPO dimer in four public water systems and 10 private drinking water wells in Parkersburg, West Virginia

Nature of the Stressor

Toxicokinetics

- Rapidly absorbed from the GI tract
- Little or no metabolism
- Elimination is rapid
  - Half-lives for beta phase in rodents are 23 – 89 **hours**
  - Half-lives for beta phase in monkeys are 64 – 80 **hours**
  - Clearance in female rodents is faster than males
- Exposure through lactation seems to be limited
- Mean blood concentrations did not increase after repeated doses



A main point here is that elimination rates are the same in both rodents and monkeys and is in hours which is very different from PFOA

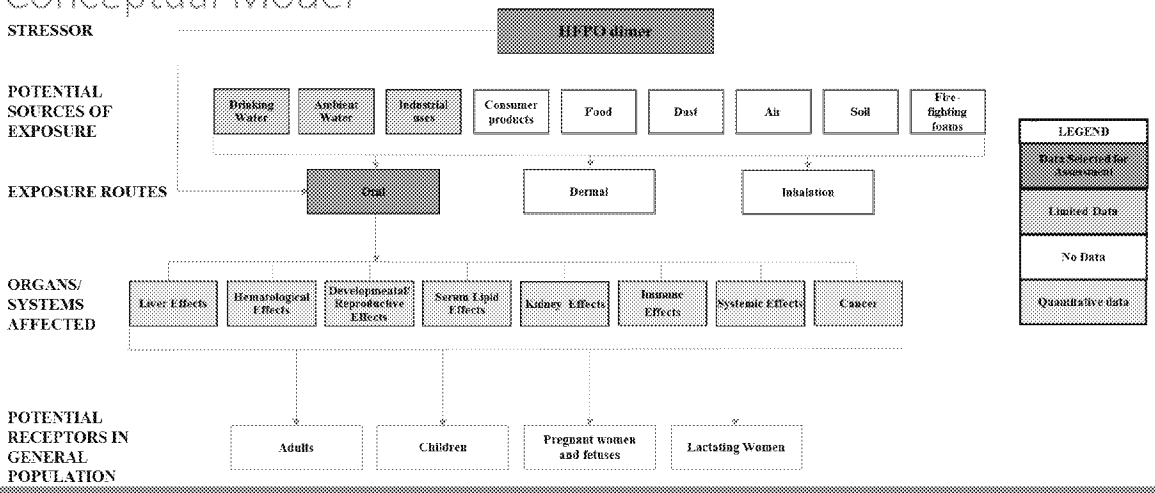
Problem Formulation

Conceptual Model

- Provides useful information to characterize and communicate the potential health risks related to exposure
  - Sources of exposure to the contaminant
  - Routes of exposure
  - Potential endpoints for the assessment (liver toxicity, developmental effects, etc.)
  - Population and life stages potentially at risk

Problem Formulation

Conceptual Model



Methods

Peer Reviewed Public Literature

- Conducted a comprehensive contractor-led search of information available in the public domain
  - Searched 4 major databases (PubMed, Toxline, WOS, TSCATS)
  - Supplemented by searching 20 other databases for health effects, toxicokinetic, and mechanistic information
- Determined potential relevance based primarily on a title and abstract screen

Literature Search Results

Publically available peer reviewed publications

- No human epidemiological studies identified
- 4 in vivo studies from the peer-reviewed primary literature
  - 28 day oral toxicity study evaluating hepatotoxic effects in mice (Wang et al., 2016)
  - 28 day oral toxicity study evaluating immunomodulatory effects in mice (Rushing et al., 2017)
  - 2 studies that are published versions of Chemours data:
    - The OECD 453 combined chronic toxicity/oncogenicity study (2 year) in rats (Rae et al., 2015)
    - An oral, single dose pharmacokinetic study describing absorption, distribution, elimination, and distribution in rats, mice and cynomolgus monkeys (Gannon et al., 2016)
- 1 *in vitro* study evaluating cytotoxicity in human liver cells (Sheng et al., 2018)

Methods

Data Submitted from Chemours

- Original Premanufacture Notices (PMN) was submitted in 2008 and included health data such as:
  - Acute and 7 day oral and dermal toxicity studies
  - 28 day oral toxicity study in mice and rats (OECD TG 407)
  - Toxicokinetic studies
  - Genotoxicity studies (*in vivo* and *in vitro*)
- EPA concluded that additional testing was required in a 2009 Consent Order:
  - One-generation reproduction study in mice (OECD 421, modified)
  - Repeated-dose metabolism and pharmacokinetics in rats and mice (OPPTS 870.7485)
  - 90-day toxicity study (OPPTS 870.3100; OECD 408)
  - Chronic toxicity/carcinogenicity study in rats (OPPTS 870.4300; OECD 408)
- Additional data was submitted as required under TSCA reporting requirements

Methods

Screening and Evaluation of Chemours Data

EPA/OPPT's 2008 Review:

- Many of the studies submitted were conducted according to OECD Test Guidelines and Principles of Good Laboratory Practices (GLP), and full study reports were submitted to EPA by Dupont/Chemours.
- The studies formed the primary basis of OPPT's 2008 assessment of potential health hazards.

Additional Data Submitted Under TSCA:

- Under the 2009 Consent Order EPA required additional testing according to OECD Test Guidelines and/or EPA Health Effects Test Guidelines for Pesticides and Toxic Substances
  - For the one-generation reproduction study in mice (OECD 421, modified), EPA included specific modifications to the test based on information for PFAS chemicals.
  - For the chronic toxicity/carcinogenicity study in rats (OPPTS 870.4300; OECD 408) , EPA reviewed and concurred with the study protocol.
- The submitter consulted with EPA on study findings to determine the need for additional data (e.g., the need for further toxicokinetic testing based on results of the first study)
- EPA review of the studies upon receipt indicated they were acceptable for their intended purpose, for use in assessing risks under TSCA.

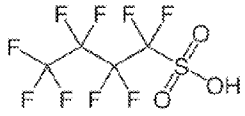
Perfluorobutane sulfonate (PFBS)

Nature of the Stressor

Background and Physical and Chemical Properties

Perfluorobutane sulfonate (PFBS) (CASRN 375-73-5) and its related salt called potassium perfluorobutane sulfonate (K+PFBS) (CASRN 29420-49-3) are manufactured for use in paints, cleaning agents, and water-impermeable products

Perfluorobutane Sulfonate



Potassium Perfluorobutane Sulfonate

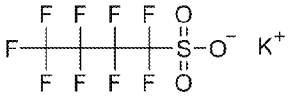


Table 1. Physicochemical Properties of PFBS (CASRN 375-73-5) and Related Compound K^+PFBS (CASRN 29420-49-3)[a]

Property (unit)	Value	
	PFBS (free acid)	K^+PFBS (potassium salt)
Boiling point (°C)	200	76–84
Density (g/cm^3 at 71°C)	ND	ND
Vapor pressure (mm Hg at 20°C)	ND	9.15×10^{-8}
pH (unitless)	ND	ND
Solubility in water (mg/L)	56.6 at 24°C	46.2 at 20°C
Molecular weight (g/mol)	300.10	338.19
Dissociation constant	NA	Fully dissociated in water over the pH range of 4–9

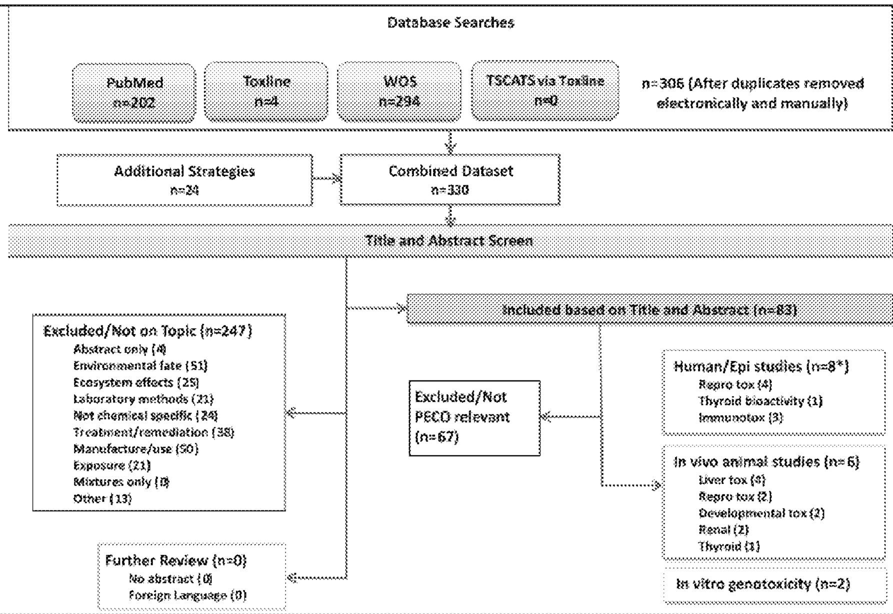
Nature of the Stressor

PFBS Toxicokinetics

Exposure regimen	Serum half-life
Varied; occupational exposure (5 male; 1 female); followed for 180 days after cessation of PFBS exposure	25.8 days (95% confidence interval = 16.6-40.2)
Cynomolgus monkey I.V. (10mg/kg)	95.2±27.1 hours (males) 83.2±41.0 hours (females)
Rat I.V. (30 mg/kg)	4.51±2.22 hours (males) 3.96±0.21 hours (females)
Rat Oral	4.68±0.43 hours (males) 7.42±0.79 hours (females)

TK information based on Olsen et al. (2009)

Methods



(Note: Some of the included studies were assigned more than one tag, so the sum of the references in boxes below "Title and Abstract screen" does not match exactly the total number of references in the "Combined Dataset".)

Literature Search Results

Publically available peer reviewed studies

EPA

Summary of Available Toxicity Information

	Hepato	Repro	Dev	DNT	Thyroid	Immuno	Renal	Genotox	Cancer
Perflourobutanesulfonate (PFBS)	4	2	2		1		2		

= human study(ies) available = mammalian animal study(ies) available

- **A 2014 PPRTV already exists; the information provided here includes the studies from the PPRTV and the literature update**
- There are 6 human epidemiological studies that provide data on potential reproductive, thyroid, or immunological effects; two of the studies also have supplemental data files
- Six *in vivo* animal studies provide potentially relevant data on various adverse effects, including liver and kidney toxicity, reproductive/developmental toxicity, and thyroid effects

Next Steps

- Review and evaluate data
- Develop draft analysis including POD(s), uncertainty factors, RfD derivation
- Update PFAS Toxicity Workgroup and present draft decisions prior to external peer review

Contacts

- GenX
  - Betsy Behl, EPA/OW, Director Health and Ecological Criteria Division in the Office of Science and Technology

    Phone: 202-566-0788

    Email: behl.betsy@epa.gov
- PFBS
  - Andrew J.R. Gillespie, Ph.D, EPA/ORD, Executive Lead for PFAS R&D

    Phone: 919-541-3655

    Email: gillespie.andrew@epa.gov